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10/533,325	05/02/2005	Gary Wayne Goodson	PU5025USW	5293
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GLAXOSMITHKLINE CORPORATE INTELLECTUAL PROPERTY, MAI B475 FIVE MOORE DR., PO BOX 13398 RESEARCH TRIANGLE PARK, NC 27709-3398			EXAMINER WESTERBERG, NISSA M	
			ART UNIT 4173	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/533,325	<b>Applicant(s)</b> GOODSON ET AL.	
	<b>Examiner</b> Nissa M. Westerberg	<b>Art Unit</b> 4173	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1 - 17 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1 - 17 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. ____.                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>5/2/05, 11/21/05</u> .  | 6) <input type="checkbox"/> Other: ____.                          |

## **DETAILED ACTION**

### ***Status of Claims***

Claims 1 – 17 are pending and currently under examination.

### ***Specification***

1. The use of the trademarks “Cab-o-Sil” (p 10, ln 11) and “Avicel” (p 15, 16, and 17) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The application relates to a composition of specific drugs and not to a generic pharmaceutical composition.

### ***Double Patenting***

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1 – 17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 16 of U.S. Patent No. 6,113,920 in view of Rudnic et al. (PGPub 2002/0068085). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed inventions are obvious to one of ordinary skill in the art.

Patent '920 discloses a combination of lamivudine or a pharmaceutically acceptable derivative thereof, zidovudine and a pharmaceutically derivative thereof and silicon dioxide present from about 0.05% to about 10% by weight.

The claims of the instant application recite a composition comprising two components, an immediate and controlled release component. The controlled release component comprises zidovudine as the active ingredient while the immediate release component comprises zidovudine and lamivudine. Glidants such as silicon dioxide are taught as optional ingredients (p 9, ln 3 – 5, p 6 ln 17 – 18 of the instant specification).

Rudnic et al. discloses a composition that contains at least two antiviral dosage forms, each with different release profiles (paragraph [0006]). The antiviral drugs suitable for use in these compositions include lamivudine and zidovudine (paragraph [0056]). The different forms with different release profiles can have the same or different antiviral drug ingredient (paragraph [0017]). When produced, the tablets can include 1.5% silicon dioxide (paragraph [0143]). Immediate and controlled release formulations with zidovudine alone are prepared (paragraphs [0060] – [0066]).

Rudnic et al. teaches an antiviral composition comprising a tablet dosage form silicon dioxide and antiviral drug composition in with multiple release profiles in which

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the multiple release profiles need not have the same drug. The combination of Rudnic et al. and the antiviral compositions taught in Patent '920, which comprise zidovudine, lamivudine and silicon dioxide, render obvious the claims of the instant Application since both references teach antiviral compositions encompassing the same ingredients.

***Claim Rejections - 35 USC § 112 1<sup>st</sup> paragraph***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1 – 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims contain the limitation “or a pharmaceutically acceptable derivative thereof” which is defined on p 4, ln 12 – 15 of the specification to include any active metabolite or residue thereof. What portion of the molecule is required for it to be active metabolite is not described. Also, what amount of the molecule is a residue is not described and a single atom could be considered a residue of the molecule.

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7. Claim 14 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of an HIV (human immunodeficiency virus) infection in a mammal, does not reasonably provide enablement for the prevention of HIV infection in a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The disclosure and claims of the application have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2nd 1400 (Fed. Cir. 1988) as to undue experimentation

The factors include:

1. The nature of the invention;
2. The breadth of the claims;
3. The predictability or unpredictability of the art;
4. The amount of direction or guidance presented;
5. The presence or absence of working examples
6. The quantity of experimentation necessary;
7. The state of the prior art; and
8. The relative skill of those skilled in the art.

Each factor is address below on the basis of comparison of the disclosure, the claims and the state of the art in the assessment of undue experimentation.

1. The nature of the invention: a method of treating or preventing an HIV infection in a mammal comprising administering a pharmaceutical composition comprising a controlled release formulation of 3'-azido-3'-deoxythymidine or a pharmaceutically acceptable salt thereof and an immediate release formulation of 3'-azido-3'-deoxythymidine or a pharmaceutically acceptable salt thereof and (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one or a pharmaceutically acceptable salt thereof.

2. The breadth of the claims: Methods of both treating and preventing an HIV infection with the aforementioned composition are encompassed by the claim.

3. The amount of direction or guidance presented, the presence or absence of working examples: Examples of pharmaceutical compositions are prepared. No experiments or results are presented for the prepared compositions to demonstrate the efficacious of the composition in preventing HIV infection.

4. The relative skill of those skilled in the art, the quantity of experimentation necessary, the state of the prior art, the predictability or unpredictability of the art: the relative skill of those skilled in the art is high. HIV is a chronic disease that can be managed through the use of drugs such as 3'-azido-3'-deoxythymidine (also known as zidovudine or AZT) and/or (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (also known as lamivudine or 3TC).

“Prevent” (p 3, dictionary.com entry, accessed 11/28/2007) is defined as to keep from happening, make impossible or to stop from being in a certain state. Therefore, the prevention of HIV means that a particular mammal will never become infected with HIV. For viral diseases, a vaccine provides immunity so that if an individual is infected, the virus does not replicate to the degree necessary to produce symptoms (p 686, col 1, paragraph 2; Robinson, HL, *Clinical Pharmacology & Therapeutics*, 82(6), p 686 – 693, 2007). Even if a patient is immunized against a virus, the patient still becomes infected with the virus. Even if a workable vaccine exists for a disease, the prevention of infection is still not realized. However, Robinson et al. discloses that research into an HIV/AIDS vaccine has thus far been unsuccessful but several vaccines are showing promise in non-human primate models (abstract). However, responses in humans have generally been less than in a non-human primate model (p 692, paragraph 3). So even if the existence of an effective vaccine would prevent infection by HIV, which it does not, the lack of an effective vaccine is further evidence that prevention of infection with HIV is currently not known in the art.

The drugs claimed have been shown to be useful for the treatment of HIV and while Applicant is enabled for a method of treatment of HIV with the claimed composition, Applicant is not enabled for a method of prevention of HIV with the claimed composition. Since the term “treating” is inclusive of various administrative timing schemes and thus provides adequate coverage for all reasonably successful therapies, the examiner recommends deleting the term “preventing” and simply reciting “treating” only instead.

***Claim Rejections - 35 USC § 112 2<sup>nd</sup> Paragraph***

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim contains the limitation “wherein the controlled release formulation releases 3'-azido-3'-deoxythymidine within 3 – 6 hours.” What marks the beginning of the time frame in which the drug is released from the formulation is not defined. Possibilities include that this time period could commence upon formulation of the pharmaceutical composition or that it could commence upon administration of the pharmaceutical composition to a subject.

9. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4, from which this claim depends, adds the limitations that “the controlled release formulation comprises a mixture of polymers.” Claim 5 recites the limitation “wherein the polymers are hydroxypropylmethylcellulose.” Mixtures contain more than one ingredient so how a mixture of polymers can contain only one element, hydroxypropylmethylcellulose, is not understood. It is noted that the specification recites that a polymer mixture of different hydroxypropylmethylcellulose

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polymers with varying viscosities maybe used (p 8, ln 7 – 8) but the specification does not define the term in that manner nor does this claim contain that limitation.

***Claim Rejections - 35 USC § 103***

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1 – 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rudnic et al. (PGPub 2002/0068085) in view of Cameron et al. (WO 92/20344).

Rudnic et al. discloses an antiviral product that contains at least two antiviral dosage forms, each with a different release profile (paragraph [0006]). These dosage forms are an improvement over those in which one antiviral dosage unit only has one release profile (paragraph [0017]). Antiviral drugs that may be used include lamivudine and zidovudine (paragraph [0056]). Each dosage form can have the same or different antiviral drug ingredients (paragraph [0017]).

This product can be administered once a day (paragraph [0016]). A unitary antiviral product contains a combination of release profiles with an immediate release tablet and two or more additional tablets that provide for the delayed release of the antiviral (paragraph [0027]). Such dosage forms could also be referred to as a tablet within a tablet. Other oral administration forms that are suitable include pellets or particles that are then formed into a tablet (paragraph [0026]).

The sustained release components can be integrated into the compositions or as coatings over the pellet or granule (paragraph [0051]). Many polymers are suitable for use in the sustained release component, including hydroxypropylmethylcellulose (paragraph [0052]). Almost all of the examples of the delayed, enteric or sustained release components (paragraphs [0060] – [0065]) contain a mixture of at least two

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polymers. When the controlled or sustained release polymer are coated on the granules (paragraph [0051]), two layers are formed so when these particles are embedded in a tablet, a bilayer or multilayer tablet is formed.

The maximum serum concentration of the drug can be reached in less than 12 hours and/or no earlier than four hours after administration (paragraph [0009]). Given this teaching, the drug can be released within 3 to 6 hours after administration to a subject.

Rudnic et al. does not disclose dosage forms using a combination of antiviral drugs, specific dosage amounts in milligrams of the antiviral drugs, the use of pharmaceutical salts of the antiviral drugs, the stereochemical form of the antiviral drugs or the use of the antiviral dosage forms for the treatment of HIV.

Cameron et al. discloses a composition that is a combination of a 1,3-oxathiolane nucleoside analog with other antiviral agents (p 1, paragraph 1). The 1,3-oxathiolane nucleoside analogs of formula I include a mixture of the (+) and (-) enantiomers (p 2). The (+) and (-) enantiomers are equipotent against HIV but the (-) enantiomer has considerably lower cytotoxicity than the (+) enantiomer. The (-) enantiomer is known as 3TC or (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (p 3, paragraph 2). The synthesis and separation of the two enantiomers are described (p 13 – 15). Using an enzymatic process that preferentially deaminates the (+) form, the (+) enantiomer was completely removed (p 13, (ii) paragraph, line 5 – 6), leaving only the (-) enantiomer.

The composition can comprise a compound of formula I or a pharmaceutically acceptable salt thereof in combination with an inhibitor such as zidovudine or a pharmaceutically acceptable derivative thereof (p 3, paragraphs 4 – 6). Acceptable derivatives include salts (p 4, paragraph 3). Among the salts exemplified are those derived from organic acids such as methanesulfonic acid (p 5, paragraph 2, ln 5). As evidenced by the product information for Sigma M0880 (accessed 12/7/2007), ethyl methanesulfonate is also known as ethyl mesylate. Therefore the salt of methanesulfonic acid, methanesulfonate, is also known as mesylate.

For each active ingredient, a dose in the range of 50 to 700 mg is disclosed (p 6, paragraph 5). A method for treatment of viral infections in a mammal (p 5, last paragraph and claim 9, p 19), including HIV (abstract), is disclosed. Figures 1 and 6 show the antiviral activity of a combination of the compound of example 1 (the (-) enantiomer of formula I, also known as 3TC and lamivudine) and AZT (also known as zidovudine) in cells infected with HIV-1.

In summary, Rudnic et al. teaches improved antiviral compositions that contain both an immediate and a controlled release component with a single antiviral agent such as zidovudine in each layer. The drug composition in the two layers may be different. Cameron et al. discloses combinations of antiviral drugs, including the combination of zidovudine and lamivudine. Given the improved antiviral composition taught by Rudnic et al. in which an immediate and at least one delayed release component and the teachings of Cameron et al. as to the efficacy of a combination of lamivudine and zidovudine, it would have been obvious to one of ordinary skill in the art

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at the time of the instant invention to combine the two teachings into one antiviral pharmaceutical composition as described in the claims of the instant application.

### ***Conclusion***

Claims 1 – 17 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 7:30 a.m. - 5 p.m. ET. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718 or Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NMW

/Ardin Marschel/  
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